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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/736,989	CUNNINGHAM ET AL.	
	Examiner	Art Unit	
	Allison M Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *21,23 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22,24-28 and 30-41* is/are rejected.

7)☒ Claim(s) *35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

In a response filed on 12/30/04 applicant elected the species of therapeutic agents, as the candidate compounds from claim 20; analgesics as the candidate compound from claim 22; and hydroxypropyl cellulose as the surface stabilizer from the combination of species listed in claims 27 and 29. Upon said elections of species, claims 21, 23 and 29 become drawn to unelected species and are withdrawn from consideration during initial prosecution.

This species election is made with traverse on the grounds that search and examination of the distinct species would not be burdensome, since a reasonable number of species may be claimed in one application. However, examiner maintains that a search and examination of all the claimed species would be burdensome because that the number of species presented in the current application is not reasonable, for example, claim 22 lists 67 distinct species and the combination of species of surface stabilizers listed in claims 27 and 29 numbers well over 100.

Status of Application

Claims 1-20, 22, 24-28 and 30-41 are being examined for patentability. Claims 1-41 are pending in the current application, of which 21, 23 and 29 have been withdrawn from consideration.

Priority

Acknowledgement is made of applicant's claim for priority to provisional application 60/433,784, filed 12/17/02.

Duplicate Claim Warning

Applicant is advised that should any one of claims 30, 36 or 41 be found allowable, the other two claims will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Though claims 30, 36 and 41 are dependent claims off of claim 1, 31 and 37, respectively, the claims do not correlate properly to the respective parent claims and each have separate and distinct steps, rendering the dependencies null; therefore claims 36 and 41 are being examined as independently claimed methods. When two or more claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Objections

Applicant's claim 35 is objected to because of a minor grammatical error; claim 9 should read, "The method of claim 1, wherein a mixture of tow or more candidate compounds are screened in step (c)."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claim 13 is directed to the method of claim 1, and further requires each of the candidate compounds to be in the form of a salt or to be conjugated to another substance to render the compound poorly soluble. A compound in the form of a salt would not render the compound poorly soluble. Instead, by definition, one of ordinary skill in the art knows that salts are ionic compounds that disassociate in water; therefore using the salt form of a compound would render a compound *more* soluble, not *poorly* soluble. Salt only renders certain compounds, such as insoluble proteins, poorly soluble in "salting out processes," such as described by Styer (Biochemistry, 1995); therefore the claim is being interpreted to mean, "wherein each of the candidate compounds is rendered poorly soluble by addition of salt in a salting out procedure." This interpretation, in itself, is further limited to only compounds that would be rendered poorly soluble by a salting out procedure, such as insoluble proteins.

Claim 13 is further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claim 13 is directed to the method of claim 1, and further requires each of the candidate compounds to be in the form of a salt or to be conjugated to another substance to render the compound poorly soluble. The term "another substance" does not adequately describe any species or genus of acceptable substances that would render the compound poorly soluble. It is not clear what limitations are encompassed in this limitation. Applicant fails to provide sufficient written description of other substances, much less sufficient description of a representative number of species which is required to claim all "other substances." Additionally, there is no disclosure of relevant, identifying characteristics, such as structure or other physical or chemical

properties, or functional characteristics, beyond disclosure of the generic action (rendering the compound poorly soluble), sufficient to show the applicant was in possession of the claimed genus. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406. See MPEP § 2163.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13, 17, 18, 20, 24, 28, 30, 36 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 13 is directed to the method of claim 1, wherein each of the candidate compounds is in the form of a salt or is conjugated to another substance to render the compound poorly soluble. First, it is not clear how a candidate compound in the form of a salt is rendered *poorly* soluble. Compounds in the form of salts are often extremely soluble, as they are composed of ions that interact freely with water. Second, it is not clear what "other substance" the candidate compound can be conjugated to in order to render the compound poorly soluble, the metes and bounds of this claim cannot be determined. Please note that the language of a claim must make it clear what subject matter the claim encompasses to adequately delineate its "metes and bounds." See, e.g., the following decisions: In re Hammack, 427 F 2d. 1378, 1382, 166 USPQ 204, 208 (CCPA 1970); In re Venezia 530 F 2d. 956, 958, 189 USPQ 149, 151 (CCPA 1976); In re Goffe, 526 F 2d. 1393, 1397, 188 USPQ 131, 135 (CCPA 1975); In re Watson, 517 F 2d. 465, 477, 186 USPQ 11, 20 (CCPA 1975); In re Knowlton 481 F 2d. 1357, 1366, 178 USPQ 486, 492 (CCPA 1973). The courts have also indicated that before claimed subject matter can properly be compared to the prior art, it is essential to know what the claims do in fact cover. See, e.g., the following decisions: In re Steele, 305 F 2d. 859, 134 USPQ 292 (CCPA 1962); In re

Moore 439 F 2d. 1232, 169 USPQ 236 (CCPA 1969); In re Merat, 519 F 2d. 1390, 186 USPQ 471 (CCPA 1975).

Applicant's claim 17 is directed to the method of claim 1, wherein one or more candidate compounds are independently present in the liquid dispersion medium at a concentration selected from the group consisting of less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, less than about 0.1%, less than about 0.01%, and less than about 0.001%. It is not clear how concentration is measured in percentage. The concentration of a solid in a solution, such as a milled candidate compound in aqueous dispersion medium, should be measured in weight/volume. The percentages do not describe the amount or concentration of candidate compound present in the dispersion. Furthermore, the term "independently present" is unclear because it appears to require that each compound, in the case where there are two or more candidate compounds in a single dispersion, be present in the specified concentrations; however, if two or more compounds are "independently present" in the dispersion at a concentration of greater then 50%, the make-up of the composition would total over 100%.

Applicant's claim 18 is directed to the method of claim 1, wherein the one or more candidate compounds are independently present in the liquid dispersion medium at a concentration selected from the group consisting of from about 99.99% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight based on the total combined dry weight of the candidate compound and at least one surface stabilizer, not including other excipients. Again, the term "independently present" is unclear because it appears to require that each compound, in the case where there are two or more candidate compounds in a single dispersion, be present in the specified concentrations by weight; however, if two or more

compounds are "independently present" in the dispersion at a concentration by weight of greater then 50%, the make-up of the composition would total over 100%.

Applicant's claim 20 is directed to the method of claim 1, wherein one or more candidate compounds are selected independently from the group consisting of therapeutic agents (elected species). It is not clear what is meant to be inferred by use of the term "selected independently." It appears as if the claim is meant to require the candidate compound to selected from the group consisting of therapeutic agents (elected species); the term "selected independently" confuses the language and misconstrues the claim.

Applicant's claim 24 is directed to the method of claim 1, wherein the at least one surface stabilizer is independently present in the liquid dispersion medium at a concentration selected from the group consisting of from about 0.01% to about 99.999%, from about 5% to about 99.9%, and from about 10% to about 99.5%, by weight based on the total combined dry weight of the candidate compound and surface stabilizer, not including other excipients. Again, the term "independently present" is unclear because it appears to require that each surface stabilizer, in the case where there are two or more surface stabilizer in a single dispersion, be present in the specified concentrations by weight; however, if two or more surface stabilizer are "independently present" in the dispersion at a concentration by weight of greater then 50%, the make-up of the composition would total over 100%.

Applicant's claim 28 requires the cationic surface stabilizers to be selected from the group that contains cellulosic. Cellulosic surface stabilizers are not cationic, they are non-ionic, as taught by Liversidge et al USP 6,221,400 (See col. 7, ln 25-32). Therefore the term is repugnant to the art.

Applicant's claim 30 is directed to the method of milling small quantities of candidate compounds of claim 1, however claim 30 does not seem to properly correlate to claim 1. Claim 30 comprises independent steps, distinct from those of claim 1, for example, claim 30 requires the

step (a) of dissolving the candidate compound in a solvent and step (c) of evaporating the solvent, which is not required in the method of claim 1. Claim 1 requires the step of (a) providing one or more candidate compounds in a liquid dispersion medium in which the candidate compound is poorly soluble, which is not required in the method of claim 30. The claimed steps do not appear to overlap or be co-extensive, rather the claims seem to be directed at distinct and independent methods. Therefore claim 30 is not being treated as a proper dependent of claim 1, but rather an independent invention.

Claim 35 recites the limitation "screened in step (c)" in the second line of the claim. There is insufficient antecedent basis for this limitation in the claim, the claim should refer to the screening in step (d).

Applicant's claim 36 is directed to the method of high throughput screening of claim 31, however claim 36 does not seem to properly correlate to claim 31. Claim 36 comprises independent steps, distinct from those of claim 31, for example, claim 31 requires the step (d) of screening the candidate compounds obtained in step (c) in a conventional high throughput screening assay to determine if one or more of the candidate compounds exhibits a desired activity, which is not required in the method of claim 36. Claim 36 requires the step of (c) evaporating the solvent, which is not required in the method of claim 31. The claimed steps do not appear to overlap or be co-extensive, rather the claims seem to be directed at distinct and independent methods. Therefore claim 36 is not being treated as a proper dependent of claim 31, but rather an independent invention.

Applicant's claim 41 is directed to the method of high throughput screening of claim 37, however claim 41 does not seem to properly correlate to claim 37. Claim 41 comprises independent steps, distinct from those of claim 37, for example, claim 37 requires the step (a) of screening one or more candidate compounds in a conventional high throughput screening assay to determine if one or more of the candidate compounds exhibits a desired activity, which is not

required in the method of claim 41. Claim 41 requires the step of (c) evaporating the solvent, which is not required in the method of claim 37. The claimed steps do not appear to overlap or be co-extensive, rather the claims seem to be directed at distinct and independent methods. Therefore claim 41 is not being treated as a proper dependent of claim 37, but rather an independent invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 7-12, 14-15, 17, 19-20, 22, 24 and 26-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Haskell (US Patent 6,814,319), in light of Chemical Land 21.com ("Celecoxib," 2005), Hercules Product Data (Klucel "Hydroxypropylcelluolose," 2003) and Na et al (US Patent 5,298,292).

Haskell teach a method of milling small a small quantity of Celecoxib, a therapeutic agent (Chemical Land21.com) (which applicant generically refers to as a candidate compound) comprising: providing a small amount of the drug in a suitable volume of an aqueous solution containing 2.5% hydroxypropyl cellulose (surface stabilizer), in which the Celecoxib is poorly soluble, so that the solution contained 20% Celecoxib; 6.0 mL of the Celecoxib solution was then dispersed in a scintillation vial in a milling apparatus in the presence of glass beads (attrition milling media); and agitating the glass beads by means of a rotating magnet for 26 to 52 minutes, the Celecoxib particles were reduced to a target size of 0.2-3 microns (200-3000 nm) (See col. 13,

ln 50- col. 14, ln 29) (Claims 1, 7, 9, 11, 14, 17, 20, 22, 24, 26). Celecoxib is an anti-inflammatory (an analgesic), it is a crystalline powder (See Chemical Land21.com) (Claim 19). Hydroxypropyl cellulose is a non-ionic surface stabilizer (See Hercules Product Data) (Claim 27). The glass beads have a size of 0.5-3.6 mm (500 microns- 3600 microns) (See Table 1, col. 14) (Claim 8).

Though the particles of the above example were only reduced to sizes down to 200 nm, Haskell teach the method can be used to reduce drug compounds down to 10 nm in size (See col. 6, ln 28-33) (Claim 14).

In the above example Celecoxib was in a 20% concentration in the liquid dispersion medium; however Haskell teach the drug concentration in the dispersion medium can be as low as 0.1% (See col. 8, ln 14-33) (Claim 17).

The surface stabilizer can be present in a concentration from 0.1% to 90%, 0.1% to 50%, or more preferably 0.1% to 25% (See col. 7, ln 28-36) (Claim 24). The surface stabilizer can be added to the liquid dispersion at any time, including before, during or after milling (See col. 6, ln 65- col. 7, ln 3). Though Haskell uses hydroxypropylcellulose in Example 1, he also teaches a wide variety of suitable surfactants that can alternatively be used including gelatin, casein, lecithin, gum acacia, cholesterol, and more (See col. 7, ln 1-23). The surface stabilizer can alternatively be sodium dodecyl sulfate, an anionic (and therefore ionic) surface stabilizer (See Na et al, abstract) (Claim 26). Exemplary cationic surface stabilizers taught by Haskell include lecithin (cationic phosphatides) (which reads on applicant's claim for a cationic phospholipid) and benzalkonium chloride (which reads on applicant's claim for a nonpolymeric compound (See col. 7, ln 1-23) (Claim 28).

Haskell further teaches the invention can be practiced with any liquid dispersion medium in which the particular drug selected is poorly soluble, including water, aqueous salt solutions, safflower oil, ethanol, t-butanol and glycol; poorly soluble is defined as having a solubility of not

greater than about 10 mg/mL, preferably not greater than 1mg/mL (See col. 6, ln 50-60) (Claims 10 & 12).

Instead of glass the grinding media can alternatively be zirconium oxide, a type of ceramic, however zirconium oxide can also be considered a polymeric material as it is an infinitely cross-linked networked polymer (Claim 7). The size of the grinding media can range in size from 0.2-5 mm in size (See col. 8, ln 35-51) (Claim 8).

Haskell teach that up to 100% of the particles prepared by his method have an average particle size (which applicant calls the effective average particle size) of less than 1000 nm (the average particle size) (See col. 6, ln 28-41) (Claim 15).

Finally, Haskell teaches the particle size reduction process can range from 9 minutes (0.15 hours) to 72 hours, wherein the length of agitation time is inversely proportionate to the end size of the particles, the longer the agitation time, the smaller the particles (See col. 11, ln 35-54) (Claim 9).

Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-8, 11, 12, 16-19 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haskell (US Patent 6,814,319).

Haskell teach a method of milling a small quantity of Celecoxib (which applicant generically refers to as a candidate compound) comprising: providing a small amount of the candidate compound in a suitable volume of an aqueous solution containing 2.5% hydroxypropyl cellulose (surface stabilizer), in which the Celecoxib is poorly soluble, so that the solution contained 20% Celecoxib; 6.0 mL of the Celecoxib solution was then dispersed in a scintillation vial in a milling apparatus in the presence of glass beads (attrition milling media); and agitating the glass beads by means of a rotating magnet for 26 to 52 minutes, the Celecoxib particles were reduced to a target size of 0.2-3 microns (200-3000 nm) (See col. 13, ln 50- col. 14, ln 29). The glass beads have a size of 0.5-3.6 mm (500 microns- 3600 microns) (See Table 1, col. 14). The surface stabilizer can be added to the liquid dispersion at any time, including before, during or after milling (See col. 6, ln 65- col. 7, ln 3).

While Haskell is silent on the possibility of milling small quantities of two or more candidate compounds simultaneously, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more candidate compounds in the reduction of step(a) (Claim 1). The skilled artisan would have been motivated to mix two or more candidate compounds in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to

grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the method of particle size reduction of Haskell works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

Haskell teach suitable grinding media can comprise glass, lead-free glass, latex and/or zirconium oxide beads, however the reference clearly indicates that the material of the grinding media can be any suitable material that is chemically inert and resistant to chipping or cracking during the process of the invention (See col. 8, ln 35-40). Therefore it would have been obvious to one of ordinary skill in the art to use steel beads as grinding media. One of ordinary skill in the art would have been motivated to use steel beads because steel is known for its strength and durability, one would not expect chipping or cracking. Additionally, one would expect success because steel is an inert metal (FeC) that would not effect the candidate compound being ground, and because Haskell teaches that he attrition milling media can be selected from any appropriate materials (Claim 7). Additionally, though Haskell teach the grinding media to range in size from 0.2 to 5 mm, the reference clearly indicates that the size of the grinding media used in the claimed composition is a result effective variable (See col. 8, ln 40-51). Smaller grinding media, with greater surface area, would be capable of reducing the drug substance (candidate compounds) to smaller sizes; therefore the size of the grinding media would be routinely optimized by one of ordinary skill in the art to sizes of less than about 200 microns, less than about 100 microns, less than about 50 microns, and mixtures thereof, in practicing the invention disclosed by Haskell (Claim 8).

Though in Example 1 Haskell teaches the total dispersion volume to be 6 mL, the reference clearly indicates that the total dispersion volume required for the particle size reduction process is a result effective variable, based on the type and size of the milling equipment used (See col. 11, ln 21-33). Therefore the total dispersion volume would be routinely optimized by

one of ordinary skill in the art to amounts of less than about 5 mL, less than about 4 mL, less than about 3 mL, less than about 2 mL, less than about 1.75 mL, less than about 1.5 mL, less than about 1.25 mL, less than about 1 mL, less than about 0.75 mL, less than about 0.5 mL, less than about 0.25 mL, or less than about 0.1 mL, in practicing the invention disclosed by Haskell, depending on the amounts of candidate compound and dispersion medium used, and the size of the vessel and mill used (Claim 11).

Haskell teach the candidate compound must be poorly soluble in the liquid dispersion medium, preferably having a solubility of less than 10 mg/mL, more preferably having a solubility of less than 1 mg/mL (See col. 3, ln 64-col. 4, ln 12). However the reference clearly indicates that the solubility of the candidate compound in the liquid dispersion medium is a result effective variable. The solubility of the candidate compound in the dispersion medium would be routinely optimized by one of ordinary skill in the art to less than about 0.1 mg/mL, when possible, in practicing the invention disclosed by Haskell (Claim 12).

Haskell teaches a variety of drug compounds that can be reduced in size using his method; he is silent, however on the structural shaping of each of the compounds. While it is known that many of the drugs listed, such as Celecoxib, are crystalline (See Chemical Land21.com), it appears that any solid compound can be used in method of Haskell, including compounds that are crystalline, semi-crystalline, semi-amorphous, or amorphous, or a mixture thereof (Claim 19). One of ordinary skill in the art would thus have been motivated to use any solid compound, with crystalline, semi-crystalline, semi-amorphous, or amorphous shape in the particle size reduction practice of Haskell. One of ordinary skill in the art would have been motivated to use any solid compound in order reduce its effective particle size for the purpose of increasing surface area, for increased bioavailability of the drugs (See col. 1, ln 13-29). One would have expected success using any solid compound with crystalline, semi-crystalline, semi-amorphous or amorphous shape because the structural shape of the original particles does not

matter, since the particles are roughly ground and milled to break up the initial structure to finer, reduced size particles. It would only be required that the candidate compounds be sufficiently solid enough to be ground and milled by the method of Haskell, but the structural shape would not inhibit the grinding/milling.

Though Haskell is silent on the amount of Celecoxib used in Example 1, he does teach that about 10 g or less, and preferably 5 g or less should be dispersed in a suitable amount of dispersion medium (See col. 3, ln 50- 62). It is clear that the quantity and concentration of candidate compound and dispersion medium required for the particle size reduction are result effective variables. The quantity of the candidate compound required for particle size reduction would be routinely optimized by one of ordinary skill in the art to less than about 100 mg, less than about 90 mg, less than about 80 mg, less than about 70 mg, less than about 60 mg, less than about 50 mg, less than about 40 mg, less than about 30 mg, less than about 25 mg, less than about 20 mg, less than about 15 mg, less than about 10 mg, less than about 5 mg, less than about 4 mg, less than about 3 mg, less than about 2 mg, less than about 1 mg, less than about 0.75 mg, less than about 0.5 mg, less than about 0.25 mg, less than about 0.1 mg, or less than about 0.05 mg, in practicing the invention disclosed by Haskell (Claim 16). Therefore the concentration of the candidate compound in the liquid dispersion medium would also vary based on the quantity of the candidate compound in the liquid dispersion medium, thus the concentration could range from less than about 70%, down to less than 0.001% (Claim 17). The quantity and concentration of candidate compound used in the invention disclosed by Haskell would be altered depending on the solubility of the candidate compound, the amount of final product desired, the amount of dispersion medium used, the size of the vessel that is to hold the candidate compound/dispersion medium mixture, and the size of the milling apparatus. Obviously, more or less candidate compound, in coordination with the appropriate amounts of surface modifier and liquid dispersion medium, would produce a greater or lesser quantity and concentration of final

nanoparticulate drug substance; therefore the quantity of candidate compound can range from 10 g to theoretically, less than 0.05 mg. Similarly, the concentration (w/w) of the candidate compound in the total dry weight of the candidate compound and surface modifier (surface stabilizer) would also be routinely optimized by one of ordinary skill in the art. The proportions of candidate compound to surface modifier (surface stabilizer) required to successful stabilize the nanoparticles would vary based on the drug substance (candidate compound) and the surface modifier (surface stabilizer) chosen, and thus could range from 0.001% to 99.99% (Claim 18).

Though in Example 1 Haskell teaches the hydroxypropylcellulose is present in a concentration of 2.5%, Haskell teaches the surface modifying agent (surface stabilizer) can be present in a total amount of about 0.1% up to 90 % by weight based on the total dry weight of the candidate compound and surface stabilizer. Thus the reference clearly indicates that the concentration of the surface stabilizer is a result effective variable, based on the tendency of the particles to agglomerate during the milling process (See col. 7, ln 28-36). Therefore the at least one surface stabilizer can be independently present in an amount from about 0.01% to about 99.999%, about 5% to about 99.9%, or about 10% to about 99.5%, by weight, based on the total dry weight of the candidate compound and surface stabilizer, not including other excipients, in practicing the invention disclosed by Haskell (Claim 24).

Finally, though Haskell does not teach the milling apparatus to comprise at least one multi-well plate, wherein the multi-well plate comprises 2 to 96 or 24 to 48 wells, and wherein each well contains a single candidate compound and the candidate compound present in each well is either the same or different, or a combination thereof as that present in other compartments of the apparatus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a milling apparatus that comprises at least one multi-well plate. One of ordinary skill in the art would have been motivated to use a milling apparatus that can simultaneously mill multiple samples, present in different wells of a multi-well plate, in order to

hasten the particle size reduction process; or if the samples are not processed simultaneously, but sequentially, a multi-well plate would at least eliminate the step of removing and reloading a single vessel after each trial. By processing multiple samples simultaneously, or in a sequential manner in which unloading and reloading steps are eliminated, one decreases processing time significantly. One would have expected success because using a multi-well plate system, as described by Haskell, does not alter the method of reducing the particle size,, rather only the apparatus used would be modified slightly to accommodate for multi-well plates (Claim 2). Furthermore, the number of wells per plate, either 2 to 96 or 24 to 48, as well as the distribution pattern of the one or more candidate compounds within the wells of the plates are obvious matters of design choice. A multi-well plate with any appropriate number of wells could be chosen based on the ability of the milling apparatus and based on the number of samples to be ground (Claims 5 and 6). The distribution pattern of the one or more candidate compounds within the wells of the plates does not affect the method of reducing the particle size; rather by processing a plate wherein each well contains the same candidate compound would produce a larger quantity of that particle candidate compound in the reduced size; alternatively, distributing two or more different candidate compounds in separate available wells would produce a variety of candidate compounds reduced in size (Claims 3 and 4). One would have been motivated to keep the plate wells homogenous or to distribute two or more candidate compounds amongst the wells in order to satisfy their various production needs, depending on what type and amount of candidate compounds are required at that time. Again, one would expect success because the contents of wells in a multiwell plate system are kept separate, therefore the distribution pattern would not effect the size reduction of the particles.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 30, 36 and 41 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Haskell (US Patent 6,814,319).

The method of claims 30, 36 and 41 comprise (a) providing one or more candidate compounds in a solvent in which the candidate compounds are dissolved, (b) distributing the dissolved candidate compounds into one or more compartments of a milling apparatus; (c) evaporating the solvent; (d) adding water or a surface stabilizer solution to the compartments of the milling apparatus; and (e) agitating the milling apparatus such that at least one of the one or more candidate compounds are reduced to an effective average particle size of less than about 2 microns.

Haskell teach a method of milling a small quantity of Celecoxib (which applicant refers to as a candidate compound) comprising: providing a small amount of the candidate compound in a suitable volume of an aqueous solution comprising hydroxypropyl cellulose (a surface stabilizer), dispersing the Celecoxib solution into a milling apparatus, and agitating the milling apparatus such that the Celecoxib particles are reduced to an average size of 0.2-3 microns (200-3000 nm (which applicant calls an effective average particle size) (See col. 13, ln 50- col. 14, ln 29).

Though Haskell does not teach first providing the Celecoxib in a solvent in which the candidate compounds are dissolved, and then evaporating the solvent, before the hydroxypropyl cellulose solution is added, it would have been obvious to one of ordinary skill in the art to first dissolve the Celecoxib in a solvent and then to evaporate the solvent; one of ordinary skill in the art would have been motivated to do so in order to facilitate distribution of the Celecoxib into the various compartments or vessels in which the milling is to take place. Applicant teaches this is the only advantage provided by performing the extra claimed steps (a) and (b) (See Specification pg. 11-12); these steps do not effect the method of milling or the outcome. Thus one of ordinary skill in the art would recognize that dispensing liquid portions of a homogenous solution (created

by the dissolution of the compound in a solvent) using a micropipettor, and then evaporating the solvent, would be more precise and easier, then measuring out dry weights of loose dry compounds. One would expect success because dissolving the compound in a solvent, distributing the compound, and then evaporating the compound would provide the same effect as distributing the compound directly, the compound is not affected during the dissolution or evaporation steps. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Haskell (US Patent 6,814,319), in view of Stryer (*Biochemistry*, 1995).

Haskell teach a method of milling a small quantity of Celecoxib (which applicant generically refers to as a candidate compound) comprising: providing a small amount of the candidate compound in a suitable volume of an aqueous solution containing 2.5% hydroxypropyl cellulose (surface stabilizer), in which the Celecoxib is poorly soluble, so that the solution contained 20% Celecoxib; 6.0 mL of the Celecoxib solution was then dispersed in a scintillation vial in a milling apparatus in the presence of glass beads (attrition milling media); and agitating the glass beads by means of a rotating magnet for 26 to 52 minutes. The Celecoxib particles were reduced to a target size of 0.2-3 microns (200-3000 nm) (See col. 13, ln 50- col. 14, ln 29). The surface stabilizer can be added to the liquid dispersion at any time, including before, during or after milling (See col. 6, ln 65- col. 7, ln 3).

Haskell teach the candidate compound must be poorly soluble in the liquid dispersion medium, preferably having a solubility of less than 10 mg/mL, more preferably having a solubility of less than 1 mg/mL (See col. 3, ln 64-col. 4, ln 12). If the candidate compound of interest is naturally soluble it would have been obvious to one of ordinary skill in the art at the time the invention was made to use any known, suitable means to decrease the solubility of the candidate compounds to make them acceptable for the media milling as described by Haskell. For example, salt can be added to lower the solubility of most proteins (See Stryer Pg 49). Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to decrease the solubility of the drug substance by any method well known in the art, including salting out the compound using salt. The skilled artisan would have been motivated to use salt to "salt out" the compound because Haskell teach that the compound must be poorly soluble in the dispersion medium in order to successfully reduce the size of the drug substance (See col. 3, ln 64- col. 4, ln 12). One would have expected success using salt to decrease the

solubility of insoluble candidate compounds, such as some proteins, because "salting out" is a well known method in the art that function due to natural hydrophobic interactions and hydrogen bonding properties. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Haskell (US Patent 6,814,319), in view of Na et al (US Patent 5,298,292).

Haskell teach a method of milling a small quantity of Celecoxib (which applicant generically refers to as a candidate compound) comprising: providing a small amount of the candidate compound in a suitable volume of an aqueous solution containing 2.5% hydroxypropyl cellulose (surface stabilizer), in which the Celecoxib is poorly soluble, so that the solution contained 20% Celecoxib; 6.0 mL of the Celecoxib solution was then dispersed in a scintillation vial in a milling apparatus in the presence of glass beads (attrition milling media); and agitating the glass beads by means of a rotating magnet for 26 to 52 minutes, the Celecoxib particles were reduced to a target size of 0.2-3 microns (200-3000 nm) (See col. 13, ln 50- col. 14, ln 29). The surface stabilizer can be added to the liquid dispersion at any time, including before, during or after milling (See col. 6, ln 65- col. 7, ln 3).

While Haskell is silent on the possibility of milling small quantities of two or more candidate compounds simultaneously, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more candidate compounds in the reduction of Claim 1 step (a). The skilled artisan would have been motivated to mix two or more candidate compounds in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the method of particle size reduction of Haskell works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

Haskell uses hydroxypropylcellulose in Example 1 and he also teaches a wide variety of suitable surfactants that can alternatively be used including gelatin, casein, lecithin, gum acacia,

cholesterol, and more that include ionic, anionic, cationic and nonionic surface stabilizers (See col. 7, ln 1-23).

Though Haskell does not explicitly teach using more then one surfaces stabilizer in the particle size reduction method, Na et al teach a similar method of reducing the size of particles in a milling process wherein a candidate compound is provided in a liquid dispersion medium in which the candidate compound is poorly soluble, comprising a surface modifier, the dispersion is distributed into a milling apparatus in the presence of grinding media to reduce the particle size of the candidate compound to an effective particle size of less than 400 nm; however, Na et al teach adding a second surfactant (which applicant calls a surface stabilizer) to act as a cloud point modifier (See col. 1, ln 45-59 & col. 3, ln 17- col. 5, ln 65) (Claim 25). The two surfactants can be added at any time during the milling process (See col. 4, ln 44-53). Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a second anionic or cationic surfactant (surface stabilizer) in the method of Haskell. One of ordinary skill in the art would have been motivated to add a second surfactant (surface stabilizer) in order to modify the cloud point of the reduced size candidate compound, thereby protecting the size during subsequent sterilization processes. One would have expected success because the method of Na et al is almost identical to that of Haskell, and Na et al teach success using the second surfactant (surface stabilizer). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Haskell (US Patent 6,814,319), in view of Wong et al (US Patent 5,587,143).

Haskell teach a method of milling a small quantity of Celecoxib (which applicant generically refers to as a candidate compound) comprising: providing a small amount of the candidate compound in a suitable volume of an aqueous solution containing 2.5% hydroxypropyl cellulose (surface stabilizer), in which the Celecoxib is poorly soluble, so that the solution contained 20% Celecoxib; 6.0 mL of the Celecoxib solution was then dispersed in a scintillation vial in a milling apparatus in the presence of glass beads (attrition milling media); and agitating the glass beads by means of a rotating magnet for 26 to 52 minutes, the Celecoxib particles were reduced to a target size of 0.2-3 microns (200-3000 nm) (See col. 13, ln 50- col. 14, ln 29). The surface stabilizer can be added to the liquid dispersion at any time, including before, during or after milling (See col. 6, ln 65- col. 7, ln 3).

While Haskell is silent on the possibility of milling small quantities of two or more candidate compounds simultaneously, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more candidate compounds in the reduction of Claim 1 step (a). The skilled artisan would have been motivated to mix two or more candidate compounds in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the method of particle size reduction of Haskell works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

Haskell uses hydroxypropylcellulose in Example 1 and he also teaches a wide variety of suitable surfactants that can alternatively be used including gelatin, casein, lecithin, gum acacia, cholesterol, and more that include ionic, anionic, cationic and nonionic surface stabilizers (See

col. 7, ln 1-23). Though Haskell does not teach specific cationic surface stabilizers comprising polymers, biopolymers, or polysaccharides, Wong et al teach a similar process of reducing particle size of therapeutic agents using cationic sodium alginate. Wong et al teach an almost identical process of reducing the size of x-ray contrast agents as taught in Haskell, comprising introducing the x-ray contrasting agent (which applicant calls the candidate compound) along with a liquid dispersion medium and grinding media, and optionally a surface modifier, into a grinding vessel; wet grinding to reduce the particle size of the agent to less than about 1000 nm (1 micron); and separating the particles and the liquid medium from the grinding vessel. If the surface modifier was not present during the wet milling, it can be admixed with the nanoparticles produced thereafter (See col. 3, ln 16-28). Wong et al further teach that sodium alginate (a polysaccharide, biopolymer, and thus polymer) can be added to the nanoparticles to act as surface active agents as preservatives (which applicant calls a cationic surface stabilizer) (See col. 7, ln 24-35) (Claim 28). Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use an alginate as a cationic surface active agent and preservative (which applicant calls a cationic surface stabilizer) in the method of Haskell. One of ordinary skill in the art would have been motivated to add an alginate (which applicant calls a cationic surface stabilizer) in order to stabilize and preserve different therapeutic agents, such as x-ray contrast agent as used in the method of Wong et al. One would have expected success because the method of Wong et al is almost identical to that of Haskell, and Wong et al teach success using an alginate as a surface active agent and preservative (which applicant calls a cationic surface stabilizer) on the x-ray contrast agents. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made

Claims 31-35 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haskell (US Patent 6,814,319), in view of Parce et al (US Patent 6,046,056).

Haskell teach a method of milling a small quantity of Celecoxib (which applicant refers to as a candidate compound) comprising: providing a small amount of the candidate compound in a suitable volume of an aqueous solution containing hydroxypropyl cellulose (surface stabilizer), in which the Celecoxib is poorly soluble; 6.0 mL of the Celecoxib solution was then dispersed in a scintillation vial in a milling apparatus in the presence of glass beads (attrition milling media); and the apparatus so that the Celecoxib particles were reduced to a target size of 0.2-3 microns (200-3000 nm) (See col. 13, ln 50- col. 14, ln 29). Haskell teaches the surface stabilizer can be added to the liquid dispersion at any time, including before, during or after milling (See col. 6, ln 65- col. 7, ln 3).

While Haskell is silent on the possibility of milling small quantities of two or more candidate compounds simultaneously, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more candidate compounds in the reduction of step (a) (Claim 1). The skilled artisan would have been motivated to mix two or more candidate compounds in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the method of particle size reduction of Haskell works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

The method of Haskell is designed to reduce the particle size of drug substances, thereby increasing their surface area, and increasing their solubility. Solubility is one of the main factors in determining the bioavailability of a drug substance, and therefore has a direct influence on the effectiveness of the drug (See Haskell col. 1, ln 13-50). Methods such as high throughput

screening can quickly test the solubility of candidate drugs, and thereby provide leads for potentially effective drug compounds (See Parce et al col. 1, ln 14-col. 2, ln 6). Though Haskell does not teach submitting the reduced size drug substance nanoparticles to a high throughput screening assay, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen the drug compounds, reduced to nanoparticulate size by the method of Haskell, for desired solubility and other desired activities (Claim 31). One of ordinary skill in the art would have been motivated to test reduced size particles produced from the milling process of Haskell in order to determine if the reduction in size, and therefore increased surface area and potentially increased solubility would allow the drug substance to be bioavailable, absorbable, and potentially effective treatment. High throughput screening is a well known method that can simultaneously test large numbers of compounds for binding activity and/or biological activity; therefore it can more quickly and efficiently test a large number of test compounds and selectively narrow down the scope to ones with the desired qualities for more thorough and intense research efforts, thus is it extremely economical. One would have expected success because conventional high throughput screening assays are well known as effective means to screen large batches of compounds for desired effects.

Specific systems, such as that described by Parce et al, are designed specifically for small volumes of test compounds to reduce space and cost requirements (See col. 2, ln 13-45). The HTS system by Parce et al is capable of screening almost any compound to determine if it has a desired activity on a variety of chemical and biochemical systems, including bioavailability, binding, signaling, enzyme-substrate interactions, receptor-ligand binding, and more (See col. 4, ln 46-col. 5, ln 2). The HTS system of Parce et al, like most HTS systems, is capable of screening a wide variety of compounds and mixtures of two or more compounds (See col. 7, ln 23-55) (Claim 35). The HTS system is capable of performing assays on whole cell systems, which can test the effect on cellular response (See col. 6, ln 1-19), as well as enzymatic assays,

which test an enzyme's activity towards its substrate (See col. 6, ln 66- col. 7, ln 16) (Claim 32). Like most HTS systems, Parce et al's design is automated, making use of robotics and computers to quickly and efficiently perform the assays (Claim 34). The HTS assay system of Parce et al is ideal for screening compounds of such small quantities and particulate size, such as those produced in the method of Haskell; therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a high throughput screening device designed specifically for microscale compounds, such as that by Parce et al. One would have been motivated to use the device of Parce et al because it is specifically designed for use with very small volumes, as are utilized in the current claimed invention, and which are produced by the method of Haskell. One would have expected success because Parce et al teach that their HTS system is capable of screening a wide variety of compounds, including pharmaceuticals, for activities such as solubility and bioavailability (See col. 4, ln 46-col. 5, ln 2).

With respect to the amount of time between steps (a-c) reducing the particle size of one or more candidate compounds to an effective particle size of less than about 2 microns (taught by Haskell) and (d) screening the candidate compounds in a conventional high throughput screening assay (taught by Parce et al), the amount of time would depend on how long the nanoparticles would remain stable at the reduced size without agglomerating. Haskell use the various surface modifiers (surface stabilizers) to prevent agglomeration and aggregation, but they are silent on how long these modifiers are effective. However, it would have been obvious to one of ordinary skill in the art to use the reduced size candidate compound particles, produced by the method of Haskell, directly in a HTS assay, as described by Parce et al (Claim 33). One of ordinary skill in the art would have motivation to use the candidate compounds directly in a high throughput screening assay in order to expedite the screening process and more quickly find a lead candidate for further testing. One would have expected success because high throughput screening can be performed at any time, additionally, the claim does not require the candidate compound to be

found effective, it only requires HTS assay to be performed, therefore the effect of the timing of the HTS assay on the candidate compound is not considered in the claimed method.

Alternatively, it would also have been obvious to one of ordinary skill in the art at the time the invention was made to first screen the raw candidate compounds in a HTS assay to determine if one or more candidate compounds exhibit a desired activity, such as described by Parce et al, and then perform the particle size reduction process of Haskell on only those candidate compounds which showed the desired activity (Claim 37). One would have been motivated to first perform the high throughput screening assay of Parce et al in order narrow the scope of candidate compounds to be milled, thus saving time and money, as high throughput screening is becoming increasingly facile and available. As stated above, the method of Parce et al is capable of performing automatic assays, enzymatic assays or whole cell assays, and assays on two or more compounds (See Parce et al col. 7, ln 23-55, col. 6, ln 1-19, and col. 6, ln 66- col. 7, ln 16) (Claims 38-40). One would expect success for the same reasons as stated above, Parce et al teach that their HTS system is capable of screening a wide variety of compounds, including pharmaceuticals, for activities such as solubility and bioavailability (See col. 4, ln 46-col. 5, ln 2), and screening prior to the particle size reduction of Haskell would have no effect on the method of Haskell, it would only reduce the number of candidate compounds to be reduced in size. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-12, 14-20, 22, 24 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al (US Patent 5,145,684), in light of ThinkerChem.com ("Danazol" 2005), Hercules Product Data (Klucel "Hydroxypropylcelluolose," 2003) and Na et al (US Patent 5,298,292), all in view of Reed et al (US Patent 6,431,478).

Liversidge et al teach a method for reducing the particle size of a drug substance (which applicant calls a candidate compound) in a mill in the presence of grinding media (which applicant calls attrition milling media) and a surface modifier (which applicant calls a surface stabilizer). The drug substance (candidate compound) is dispersed in an aqueous liquid dispersion medium in which the drug substance (candidate compound) is poorly soluble; mechanical means, in the presence of grinding media (attrition media), are applied to reduce the particle size of the drug substance (candidate compound) to an effective average particle size of less than 400 nm. The surface modifier (surface stabilizer) adsorbs onto the surface of the particles and hinders the flocculation and/or agglomeration of the nanoparticles by acting as a mechanical or steric barrier between particles (See col. 8, ln 21-33). Particles can be reduced in the presence of the surface modifier, or the particles can be contacted with the surface modifier after attrition (See col. 2, ln 32- 56) (Claim 1 (a) and (c)).

Liversidge et al teach the drug substance (candidate compound) can be selected from a wide range of known drugs, including therapeutic agents including analgesics (See col. 3, ln 53- col. 4, ln 14) (Claims 20 & 22). It is preferred, though not required, that the drug compound be in an essentially pure form (See col. 3, ln 38-40). However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more drug substances (candidate compounds) in the reduction process of Liversidge et al. The skilled artisan would have been motivated to mix two or more drug substances (candidate compounds) in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the

mixture of nanoparticles in the same aliquot. One would have expected success because the media mill of Liversidge et al works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

Liversidge et al teach the material of the grinding media is not critical, but suggests materials such as glass beads, stainless steel or zirconium silicate, the zirconium silicate can be considered either a ceramic or a polymeric material due to its infinitely cross-linked networked polymer structure (See col. 6, ln 18-48) (Claim 7). Liversidge et al teach that the grinding media should have an average size of less than 3 mm, preferably less than 1 mm (See col. 6, ln 32-40). In Example 1, Liversidge et al use glass beads as small as 0.5 mm (500 microns) (See col. 9, ln 28). While this reads on applicant's claim for the attrition milling media to be about 500 microns, applicant further claims the milling media to be substantially smaller; however, the reference clearly indicates that the size of the grinding media used in the claimed composition is a result effective variable. Finer grinding media, with greater surface area, would be capable of reducing the drug substance (candidate compounds) to smaller sizes; therefore the size of the grinding media would be routinely optimized by one of ordinary skill in the art to sizes of less than about 500 microns, less than about 200 microns, less than about 100 microns, less than about 50 microns, and mixtures thereof, in practicing the invention disclosed by Liversidge et al (Claim 8).

Liversidge et al teach the drug substance (candidate compound) must be poorly soluble in the liquid dispersion medium, its solubility must be 10 mg/mL or less, preferably 1 mg/mL or less. However the reference clearly indicates that the solubility of the candidate compound in the liquid dispersion medium is a result effective variable. The solubility of the candidate compound in the dispersion medium would be routinely optimized by one of ordinary skill in the art to less than about 0.1 mg/mL, when possible, in practicing the invention disclosed by Liversidge et al (Claim 12).

Liversidge et al teach the drug substance (candidate compound) in the liquid dispersion medium should be from about 0.1 to 60%, preferably from 5 to 30%, by weight (See col. 5, ln 62-66). In Example 1 Liversidge et al create a premix with 327g of the crystalline drug substance Danazol (candidate compound), which is a 30% concentration (See col. 8, ln 40- col. 9, ln 16 & Thinkerchem.com) (Claims 17 & 19). The drug substance Danazol comprised 74% (w/w) of the total dry weight of the drug substance (candidate compound) and surface modifier (surface stabilizer) (Claim 18). However, in Example 2, Liversidge et al create a premix containing 10.8 g Danazol, which is only a 0.05% concentration of the entire premix, and 76.9% of the total dry weight of the drug substance and surface modifier (See col. 9, ln 19-57) (Claims 17 & 18). Liversidge et al teach the quantity and concentration of the drug substance can vary significantly from 0.1-60% (w/w) (See col. 5, ln 62-66); this clearly indicates that the various quantity and concentration of the drug substance (candidate compound) used in the claimed composition is a result effective variable, it would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by Liversidge et al. The proportion and quantity of drug substance (candidate compound) used in the invention disclosed by Liversidge et al would be altered depending on the amount of final product needed (Claims 16-18). Obviously, more drug substance, in coordination with the appropriate amounts of surface modifier and liquid dispersion medium, would produce a greater quantity of final nanoparticulate drug substance; therefore the quantity of drug substance (candidate compound) can range from over 300 g, as in Example 1, to, theoretically, less than 1 mg (Claim 16). Similarly, the concentration (w/w) of the drug substance (candidate compound) in the total dry weight of the drug substance (candidate compound) and surface modifier (surface stabilizer) would also be routinely optimized by one of ordinary skill in the art. The proportions of drug substance (candidate compound) to surface modifier (surface stabilizer) required to successful stabilize the nanoparticles would vary based on the drug substance (candidate compound) and the surface modifier (surface stabilizer) chosen. In their

working examples Liversidge et al chose Danazol as the drug substance (candidate compound) and polyvinylpyrrolidone (PVP) as the surface modifier (surface stabilizer), Danazol constituted approximately 77% of the total dry weight of the drug substance (candidate compound) and surface modifier (surface stabilizer) in all examples. This was clearly the optimized proportion for this combination; however the various proportions and amounts of the drug substance (candidate compound) used in the composition is a result effective variable, it would be routinely optimized by one of ordinary skill in the art based on the combination of elements (Claim 18).

Liversidge et al teach suitable dispersion mediums include water, aqueous salt solutions, safflower oil, ethanol, t-butanol, hexane and glycol (See col. 3, ln 38-52) (Claim 10). In Example 1, Liversidge et al use 664 mL of water, in Example 2 only 201.96 ml of water are used, the references clearly indicate that the various proportions and amounts of dispersion media used in the claimed composition is a result effective variable. The amount of liquid dispersion media used depends on how much drug substance (candidate compound) and surface modifier (surface stabilizer) are used. Therefore the amount of liquid dispersion medium can range from over 600 mL to less than 2 mL, the amount would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by Liversidge to be as low as 0.1 mL (Claim 11).

Liversidge et al teach a variety of suitable surface modifiers (surface stabilizers) including gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride (a cationic, and thus ionic surface stabilizer, See Specification, Pg. 33), calcium stearate, glycerol monostearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxides, phosphates, sodium dodecylsulfate (an anionic, and thus ionic, surface stabilizer, See Na et al), methylcellulose, hydroxyethlecellulose, hydroxypropylcellulose (a non-ionic surface stabilizer, See Hercules Product Data), and more (See col. 4, ln 28- col. 5, ln 12) (Claims 26 & 27). It is clear from the quite exhaustive list that any of the stated surface modifiers, or any

obvious variation or substitution would have been obvious to one of ordinary skill in the art at the time the invention was made, with sufficient expectation of success. Liversidge et al teach the surface modifier should be present in an amount from about 0.1% to about 90%, preferably from about 1% to about 75%, more preferably from about 20% to about 60%, based on the total dry weight of the drug substance (candidate compound) and surface modifier (surface stabilizer) (See col. 5, ln 66-col. 6, ln 5). In Example 1, Liversidge et al use 98 g PVP (surface modifier) and 327 g Danazol (drug substance); the surface modifier constituted 24 % (w/w) of the total dry weight (See col. 8, ln 40- col. 9, ln 16) (Claim 24).

Liversidge et al teach that the time required for the particle size reduction process can vary greatly, and is dependent on the processing conditions selected. Times can range from 1 minute up to over one day (See col. 6, ln 49-56). In Example 1, Liversidge et al allow the Danazol, PVP, water slurry to recirculate for 4 hours (240 minutes) (See col. 8, ln 40- col. 9, ln 16). However, as the reference clearly indicates, the amount of time the milling (reduction process) is allowed to proceed is a result effective variable, it would be routinely optimized by one of ordinary skill in the art practicing the invention disclosed by Liversidge et al. The longer the milling proceeds, the smaller the particles will be, due to increased amount of mechanical grinding they are exposed to; therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to alter the time the particles were in the grinding or milling (reduction process) in order to achieve different desired sizes of nanoparticles. Thus, the time can range from over 4 hours, as done by Liversidge et al, or can be as short as 15 minutes or less (Claim 9). The length of time required by the reduction process also depends on the strength of the mechanical force, caused by the amount of agitation and attrition in the milling (reduction process).

The method of Liversidge et al can reduces the drug substance (candidate compound) to an effective average particle size of at least less than 400 nm, some embodiments produced an

effective average particle size of less than 250 nm, and some produced an effective average particle size of less than 100 nm. However, the reference clearly indicates that the resulting effective average particle size is a result effective variable, controlled by agitation time and mechanical force. The effective average particle size could routinely be optimized by one of ordinary skill in the art to be less then 50 nm (Claim 14). By "effective average particle size" Liversidge et al required at least 90%, preferably at least 95%, and more preferably at least 99% of the particles have that weight average particle size (See col. 5, ln 20-40) (Claim 15).

The procedure of Liversidge et al was performed on a slightly larger mill then described by applicant in the current application. Though the size of the mill the components in the method may be result dependent variables, and would have been optimized by one of ordinary skill in the art when using the invention disclosed by Liversidge et al, it would have also been obvious to the skilled artisan at the time the current invention was made to perform the procedure of Liversidge et al on a small-scale mill, such as that disclosed by Reed et al. Reed et al teach a small-scale or micro media-mill that can be used to reduce the size of pharmaceutical products to a size ranging from microns to nanometers (See col. 4, ln 21-35). The reduced size and scale of the micro media-mill requires it to utilize smaller grinding media, and smaller quantities of dispersion media and candidate compounds. Specifically, the small-scale mill of Reeds et al uses polymeric, polystyrene or cross-linked polystyrene having an diameter of no greater than 500 microns, 200 microns, 50 microns, and mixtures thereof as the attrition milling media (Claims 7 & 8). The #1 and #2 sized small-scale mills of Reed et al are designed to receive approximately 8-12 mL of dispersion volume (Claim 1 (b)). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Liversidge et al's procedure of preparing a stable dispersion of nanoparticles by wet milling in presence of grinding media in conjunction with a surface modifier (surface stabilizer), using the small-scale mill of Reed et al, wherein the dispersion volume would be limited to less than 15 mL. One would have been motivated to

perform the process of Liversidge et al in the small-scale mill of Reed et al in order to perform small-scale millings when the amount of drug substance (candidate compounds) is limited, due to high cost or low availability of some drugs. One would have expected success because the small-scale mill of Reed et al is designed to reduce particle size of pharmaceuticals, and would be extremely appropriate for the application of Liversidge et al's method.

Finally, though neither Liversidge et al nor Reed et al teach the respective milling apparatuses to comprise at least one multi-well plate, wherein the multi-well plate comprises 2 to 96 or 24 to 48 wells, and wherein each well contains a single candidate compound and the candidate compound present in each well is either the same or different, or a combination thereof as that present in other compartments of the apparatus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the small scale milling apparatus of Reed et al to comprises at least one multi-well plate. One of ordinary skill in the art would have been motivated to modify the milling apparatus of Reed et al to simultaneously mill multiple samples, present in different wells of a multi-well plate, in order to hasten the particle size reduction process; or if the samples are not to be processed simultaneously, but sequentially, a multi-well plate would at least eliminate the step of removing and reloading a single vessel after each trial. By processing multiple samples simultaneously, or in a sequential manner in which unloading and reloading steps are eliminated, one decreases processing time significantly. One would have expected success because using a multi-well plate system, as described by Liversidge et al, does not alter the method of reducing the particle size, rather only the small-scale apparatus of Reed et al would be modified slightly to accommodate for multi-well plates (Claim 2). Furthermore, the number of wells per plate, either 2 to 96 or 24 to 48, as well as the distribution pattern of the one or more candidate compounds within the wells of the plates are obvious matters of design choice. A multi-well plate with any appropriate number of wells could be chosen based on the ability of the milling apparatus and based on the number of samples to be ground (Claims

5 and 6). The distribution pattern of the one or more candidate compounds within the wells of the plates does not affect the method of reducing the particle size; rather by processing a plate wherein each well contains the same candidate compound would produce a larger quantity of that particle candidate compound in the reduced size; alternatively, distributing two or more different candidate compounds in separate available wells would produce a variety of candidate compounds reduced in size (Claims 3 and 4). One would have been motivated to keep the plate wells homogenous or to distribute two or more candidate compounds amongst the wells in order to satisfy their various production needs, depending on what type and amount of candidate compounds are required at that time. Again, one would expect success because the contents of wells in a multiwell plate system are kept separate, therefore the distribution pattern would not effect the size reduction of the particles.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al (US Patent 5,145,684), in view of Na et al (US Patent 5,298,292).

Liversidge et al teach a method of milling a small quantity of a drug substance (which applicant refers to as a candidate compound) comprising: providing a small amount of the drug substance (candidate compound) in a suitable volume of an aqueous solution comprising a surface modifier (which applicant refers to as a surface stabilizer), dispersing the drug substance solution (candidate compound solution) into a milling apparatus, and agitating the milling apparatus such that the drug substance particles are reduced to an effective average particle size of less than 400 nm (See col. 2, ln 47-56).

Liversidge et al teach it is preferred, though not required, that the drug compound be in an essentially pure form (See col. 3, ln 38-40). However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more drug substances (candidate compounds) in the reduction process of Liversidge et al. The skilled artisan would have been motivated to mix two or more drug substances (candidate compounds) in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the media mill of Liversidge et al works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

The procedure of Liversidge et al was performed on a slightly larger mill then described by applicant in the current application. Though the size of the mill the components in the method may be result dependent variables, and would have been optimized by one of ordinary skill in the art when using the invention disclosed by Liversidge et al, it would have also been obvious to the skilled artisan at the time the current invention was made to perform the procedure of Liversidge

et al on a small-scale mill, such as that disclosed by Reed et al. Reed et al teach a small-scale or micro media-mill that can be used to reduce the size of pharmaceutical products to a size ranging from microns to nanometers (See col. 4, ln 21-35). The reduced size and scale of the micro media-mill requires it to utilize smaller grinding media, and smaller quantities of dispersion media and candidate compounds. The #1 and #2 sized small-scale mills of Reed et al are designed to receive approximately 8-12 mL of dispersion volume. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Liversidge et al's procedure of preparing a stable dispersion of nanoparticles by wet milling in presence of grinding media in conjunction with a surface modifier (surface stabilizer), using the small-scale mill of Reed et al, wherein the dispersion volume would be limited to less than 15 mL. One would have been motivated to perform the process of Liversidge et al in the small-scale mill of Reed et al in order to perform small-scale millings when the amount of drug substance (candidate compounds) is limited, due to high cost or low availability of some drugs. One would have expected success because the small-scale mill of Reed et al is designed to reduce particle size of pharmaceuticals, and would be extremely appropriate for the application of Liversidge et al's method.

Liversidge et al teach a variety of surfactants that can be used as surface modifiers (which applicant calls surface stabilizers), including hydroxypropylcellulose, gelatin, casein, lecithin, gum acacia, cholesterol, and more that include ionic, anionic, cationic and nonionic surface stabilizers (See col. 4, ln 34-col.5, ln 13).

Though Liversidge et al does not explicitly teach using more then one surfaces stabilizer in the particle size reduction method, Na et al teach a similar method of reducing the size of particles in a milling process wherein a candidate compound is provided in a liquid dispersion medium in which the candidate compound is poorly soluble, comprising a surface modifier, the dispersion is distributed into a milling apparatus in the presence of grinding media to reduce the particle size of the candidate compound to an effective particle size of less than 400 nm; however,

Na et al teach adding a second surfactant (which applicant calls a surface stabilizer) to act as a cloud point modifier (See col. 1, ln 45-59 & col. 3, ln 17- col. 5, ln 65) (Claim 25). The two surfactants can be added at any time during the milling process (See col. 4, ln 44-53). Na et al teaches the addition of the second surfactant can adjust the cloud point of the reduced size particles, and can help maintain the reduced size during subsequent sterilization. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a second anionic or cationic surfactant (surface stabilizer) in the method of Liversidge et al, as performed on a small scale mill of Reed et al. One of ordinary skill in the art would have been motivated to add a second surfactant (surface stabilizer) in order to modify the cloud point of the reduced size candidate compound, thereby protecting the size during subsequent sterilization processes. One would have expected success because the method of Na et al is almost identical to that of Liversidge et al, and Na et al teach success using the second surfactant (surface stabilizer). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al (US Patent 5,145,684), in view of Wong et al (US Patent 5,587,143).

Liversidge et al teach a method of milling a small quantity of a drug substance (which applicant refers to as a candidate compound) comprising: providing a small amount of the drug substance (candidate compound) in a suitable volume of an aqueous solution comprising a surface modifier (which applicant refers to as a surface stabilizer), dispersing the drug substance solution (candidate compound solution) into a milling apparatus, and agitating the milling apparatus such that the drug substance particles are reduced to an effective average particle size of less than 400 nm (See col. 2, ln 47-56).

Liversidge et al teach it is preferred, though not required, that the drug compound be in an essentially pure form (See col. 3, ln 38-40). However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more drug substances (candidate compounds) in the reduction process of Liversidge et al. The skilled artisan would have been motivated to mix two or more drug substances (candidate compounds) in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the media mill of Liversidge et al works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

The procedure of Liversidge et al was performed on a slightly larger mill then described by applicant in the current application. Though the size of the mill the components in the method may be result dependent variables, and would have been optimized by one of ordinary skill in the art when using the invention disclosed by Liversidge et al, it would have also been obvious to the skilled artisan at the time the current invention was made to perform the procedure of Liversidge

et al on a small-scale mill, such as that disclosed by Reed et al. Reed et al teach a small-scale or micro media-mill that can be used to reduce the size of pharmaceutical products to a size ranging from microns to nanometers (See col. 4, ln 21-35). The reduced size and scale of the micro media-mill requires it to utilize smaller grinding media, and smaller quantities of dispersion media and candidate compounds. The #1 and #2 sized small-scale mills of Reed et al are designed to receive approximately 8-12 mL of dispersion volume. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Liversidge et al's procedure of preparing a stable dispersion of nanoparticles by wet milling in presence of grinding media in conjunction with a surface modifier (surface stabilizer), using the small-scale mill of Reed et al, wherein the dispersion volume would be limited to less than 15 mL. One would have been motivated to perform the process of Liversidge et al in the small-scale mill of Reed et al in order to perform small-scale millings when the amount of drug substance (candidate compounds) is limited, due to high cost or low availability of some drugs. One would have expected success because the small-scale mill of Reed et al is designed to reduce particle size of pharmaceuticals, and would be extremely appropriate for the application of Liversidge et al's method.

Liversidge et al teach a variety of surfactants that can be used as surface modifiers (which applicant calls surface stabilizers), including hydroxypropylcellulose, gelatin, casein, lecithin, gum acacia, cholesterol, and more that include ionic, anionic, cationic and nonionic surface stabilizers (See col. 4, ln 34-col.5, ln 13). Though Liversidge et al do not teach specific cationic surface stabilizers comprising polymers, biopolymers, or polysaccharides, Wong et al teach a similar process of reducing particle size of therapeutic agents using cationic sodium alginate. Wong et al teach an almost identical process of reducing the size of x-ray contrast agents as taught in Liversidge et al, comprising introducing the x-ray contrasting agent (which applicant calls the candidate compound) along with a liquid dispersion medium and grinding media, and optionally a surface modifier, into a grinding vessel; wet grinding to reduce the particle size of

the agent to less than about 1000 nm (1 micron); and separating the particles and the liquid medium from the grinding vessel. If the surface modifier was not present during the wet milling, it can be admixed with the nanoparticles produced thereafter (See col. 3, ln 16-28). Wong et al further teach that sodium alginate (a polysaccharide, biopolymer, and thus polymer) can be added to the nanoparticles to act as surface active agents as preservatives (which applicant calls a cationic surface stabilizer) (See col. 7, ln 24-35) (Claim 28). Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use an alginate as a cationic surface active agent and preservative (which applicant calls a cationic surface stabilizer) in the method of Liversidge et al, as performed on a small scale mill of Reed et al. One of ordinary skill in the art would have been motivated to add an alginate (which applicant calls a cationic surface stabilizer) in order to stabilize and preserve different therapeutic agents, such as x-ray contrast agent as used in the method of Wong et al. One would have expected success because the method of Wong et al is almost identical to that of Liversidge et al, and Wong et al teach success using an alginate as a surface active agent and preservative (which applicant calls a cationic surface stabilizer) on the x-ray contrast agents. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made

Claims 30, 36 and 41 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al (US Patent 5,145,684).

The method of claims 30, 36 and 41 comprise (a) providing one or more candidate compounds in a solvent in which the candidate compounds are dissolved, (b) distributing the dissolved candidate compounds into one or more compartments of a milling apparatus; (c) evaporating the solvent; (d) adding water or a surface stabilizer solution to the compartments of the milling apparatus; and (e) agitating the milling apparatus such that at least one of the one or more candidate compounds are reduced to an effective average particle size of less than about 2 microns.

Liversidge et al teach it is preferred, though not required, that the drug compound be in an essentially pure form (See col. 3, ln 38-40). However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more drug substances (candidate compounds) in the reduction process of Liversidge et al. The skilled artisan would have been motivated to mix two or more drug substances (candidate compounds) in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the media mill of Liversidge et al works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

Liversidge et al teach a method of milling a small quantity of a drug substance (which applicant refers to as a candidate compound) comprising: providing a small amount of the drug substance (candidate compound) in a suitable volume of an aqueous solution comprising a surface modifier (which applicant refers to as a surface stabilizer), dispersing the drug substance solution (candidate compound solution) into a milling apparatus, and agitating the milling

apparatus such that the drug substance particles are reduced to an effective average particle size of less than 400 nm (See col. 2, ln 47-56).

Though Liversidge et al do not teach first providing the drug substance (candidate compound) in a solvent in which the drug substance (candidate compounds) are dissolved, and then evaporating the solvent, before the surface modifier (surface stabilizer) solution is added, it would have been obvious to one of ordinary skill in the art to first dissolve the drug substance (candidate compounds) in a solvent and then to evaporate the solvent; one of ordinary skill in the art would have been motivated to do so in order to facilitate distribution of the drug substance (candidate compounds) into the various compartments or vessels in which the milling is to take place. Applicant teaches this is the only advantage provided by performing the extra claimed steps (a) and (b) of claims 30, 36 and 41 (See Specification pg. 11-12); these steps do not effect the method of milling or the outcome. Thus one of ordinary skill in the art would recognize that dispensing liquid portions of a homogenous solution (created by the dissolution of the compound in a solvent) using a micropipettor, and then evaporating the solvent, would be more precise and easier, then measuring out dry weights of loose dry compounds. One would expect success because dissolving the compound in a solvent, distributing the compound, and then evaporating the compound would provide the same effect as distributing the compound directly, the compound is not affected during the dissolution or evaporation steps. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al (US Patent 5,145,684), in view of Reed et al (US Patent 6,431,478), further in view of Stryer (*Biochemistry*, 1995).

Liversidge et al teach a method of milling a small quantity of a drug substance (which applicant refers to as a candidate compound) comprising: providing a small amount of the drug substance (candidate compound) in a suitable volume of an aqueous solution comprising a surface modifier (which applicant refers to as a surface stabilizer), dispersing the drug substance solution (candidate compound solution) into a milling apparatus, and agitating the milling apparatus such that the drug substance particles are reduced to an effective average particle size of less than 400 nm (See col. 2, ln 47-56).

Liversidge et al teach it is preferred, though not required, that the drug compound be in an essentially pure form (See col. 3, ln 38-40). However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more drug substances (candidate compounds) in the reduction process of Liversidge et al. The skilled artisan would have been motivated to mix two or more drug substances (candidate compounds) in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the media mill of Liversidge et al works by mechanical means, it does not differentiate on the contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

The procedure of Liversidge et al was performed on a slightly larger mill then described by applicant in the current application. Though the size of the mill the components in the method may be result dependent variables, and would have been optimized by one of ordinary skill in the art when using the invention disclosed by Liversidge et al, it would have also been obvious to the

skilled artisan at the time the current invention was made to perform the procedure of Liversidge et al on a small-scale mill, such as that disclosed by Reed et al. Reed et al teach a small-scale or micro media-mill that can be used to reduce the size of pharmaceutical products to a size ranging from microns to nanometers (See col. 4, ln 21-35). The reduced size and scale of the micro media-mill requires it to utilize smaller grinding media, and smaller quantities of dispersion media and candidate compounds. The #1 and #2 sized small-scale mills of Reed et al are designed to receive approximately 8-12 mL of dispersion volume. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Liversidge et al's procedure of preparing a stable dispersion of nanoparticles by wet milling in presence of grinding media in conjunction with a surface modifier (surface stabilizer), using the small-scale mill of Reed et al, wherein the dispersion volume would be limited to less than 15 mL. One would have been motivated to perform the process of Liversidge et al in the small-scale mill of Reed et al in order to perform small-scale millings when the amount of drug substance (candidate compounds) is limited, due to high cost or low availability of some drugs. One would have expected success because the small-scale mill of Reed et al is designed to reduce particle size of pharmaceuticals, and would be extremely appropriate for the application of Liversidge et al's method.

Liversidge et al teach the candidate compound must be poorly soluble in the liquid dispersion medium, preferably having a solubility of less than 10 mg/mL, more preferably having a solubility of less than 1 mg/mL (See col. 3, ln 38-52). If the candidate compound of interest is naturally soluble it would have been obvious to one of ordinary skill in the art at the time the invention was made to use any known, suitable means to decrease the solubility of the candidate compounds to make them acceptable for the media milling as described by Liversidge et al, in the small scale mill of Reed et al. For example, salt can be added to lower the solubility of most proteins (See Stryer Pg 49). Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to decrease the solubility of the drug substance by any

method well known in the art, including salting out the compound using salt. The skilled artisan would have been motivated to use salt to "salt out" the compound because Liversidge et al teach that the compound must be poorly soluble in the dispersion medium in order to successfully reduce the size of the drug substance (See col. 3, ln 38-52). One would have expected success using salt to decrease the solubility of insoluble candidate compounds, such as some proteins, because "salting out" is a well known method in the art that function due to natural hydrophobic interactions and hydrogen bonding properties. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 31-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al (US Patent 5,145,684), in view of Reed et al (US Patent 6,431,478), further in view of Parce et al (US Patent 6,046,056).

Liversidge et al teach a method for reducing the particle size of a drug substance (which applicant calls a candidate compound) in a mill in the presence of grinding media (which applicant calls attrition milling media) and a surface modifier (which applicant calls a surface stabilizer). The drug substance (candidate compound) is dispersed in an aqueous liquid dispersion medium in which the drug substance (candidate compound) is poorly soluble; mechanical means, in the presence of grinding media (attrition media), are applied to reduce the particle size of the drug substance (candidate compound) to an effective average particle size of less than 400 nm. The surface modifier (surface stabilizer) adsorbs onto the surface of the particles and hinders the flocculation and/or agglomeration of the nanoparticles by acting as a mechanical or steric barrier between particles (See col. 8, ln 21-33). Particles can be reduced in the presence of the surface modifier, or the particles can be contacted with the surface modifier after attrition (See col. 2, ln 32- 56) (Claim 1 (a) and (c)).

Liversidge et al teach it is preferred, though not required, that the drug compound be in an essentially pure form (See col. 3, ln 38-40). However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a mixture of two or more drug substances (candidate compounds) in the reduction process of Liversidge et al. The skilled artisan would have been motivated to mix two or more drug substances (candidate compounds) in order to create a drug cocktail that could be tested for potential treatment. If two or more drugs were intended to act together it would have been obvious to grind them together and obtain the mixture of nanoparticles in the same aliquot. One would have expected success because the media mill of Liversidge et al works by mechanical means, it does not differentiate on the

contents of the media, therefore it would grind one pure compound the same as it would grind a mixture of two or more compounds.

The procedure of Liversidge et al was performed on a slightly larger mill then described by applicant in the current application. Though the size of the mill the components in the method may be result dependent variables, and would have been optimized by one of ordinary skill in the art when using the invention disclosed by Liversidge et al, it would have also been obvious to the skilled artisan at the time the current invention was made to perform the procedure of Liversidge et al on a small-scale mill, such as that disclosed by Reed et al. Reed et al teach a small-scale or micro media-mill that can be used to reduce the size of pharmaceutical products to a size ranging from microns to nanometers (See col. 4, ln 21-35). The reduced size and scale of the micro media-mill requires it to utilize smaller grinding media, and smaller quantities of dispersion media and candidate compounds. Specifically, the small-scale mill of Reeds et al uses polymeric, polystyrene or cross-linked polystyrene having an diameter of no greater than 500 microns, 200 microns, 50 microns, and mixtures thereof as the attrition milling media (Claims 7 & 8). The #1 and #2 sized small-scale mills of Reed et al are designed to receive approximately 8-12 mL of dispersion volume (Claim 1 (b)). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use Liversidge et al's procedure of preparing a stable dispersion of nanoparticles by wet milling in presence of grinding media in conjunction with a surface modifier (surface stabilizer), using the small-scale mill of Reed et al, wherein the dispersion volume would be limited to less than 15 mL. One would have been motivated to perform the process of Liversidge et al in the small-scale mill of Reed et al in order to perform small-scale millings when the amount of drug substance (candidate compounds) is limited, due to high cost or low availability of some drugs. One would have expected success because the small-scale mill of Reed et al is designed to reduce particle size of pharmaceuticals, and would be extremely appropriate for the application of Liversidge et al's method.

The method of Liversidge et al is designed to reduce the particle size of drug substances, thereby increasing their surface area, and increasing their solubility. Solubility is one of the main factors in determining the bioavailability of a drug substance, and therefore has a direct influence on the effectiveness of the drug (See Liversidge et al col. 1, ln 13-50). Methods such as high throughput screening can quickly test the solubility of candidate drugs, and thereby provide leads for potentially effective drug compounds (See Parce et al col. 1, ln 14-col. 2, ln 6). Though Liversidge et al do not teach submitting the reduced size drug substance nanoparticles to a high throughput screening assay, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen the drug compounds, reduced to nanoparticulate size by the method of Liversidge et al on the small scale mill of Reed et al, for desired solubility and other desired activities (Claim 31). One of ordinary skill in the art would have been motivated to test the reduced size nanoparticles produced from the milling process of Liversidge et al on the small scale mill of Reed et al in order to determine if the reduction in size, and therefore increased surface area and potentially increased solubility would allow the drug substance to be bioavailable, absorbable, and potentially effective treatment. High throughput screening is a well known method that can simultaneously test large numbers of compounds for binding activity and/or biological activity; therefore it can more quickly and efficiently test a large number of test compounds and selectively narrow down the scope to ones with the desired qualities for more thorough and intense research efforts, thus is it extremely economical. One would have expected success because conventional high throughput screening assays are well known as effective means to screen large batches of compounds for desired effects.

Specific systems, such as that described by Parce et al, are designed specifically for small volumes of test compounds to reduce space and cost requirements (See col. 2, ln 13-45). The HTS system by Parce et al is capable of screening almost any compound to determine if it has a desired activity on a variety of chemical and biochemical systems, including bioavailability,

binding, signaling, enzyme-substrate interactions, receptor-ligand binding, and more (See col. 4, ln 46-col. 5, ln 2). The HTS system of Parce et al, like most HTS systems, is capable of screening a wide variety of compounds and mixtures of two or more compounds (See col. 7, ln 23-55) (Claim 35). The HTS system is capable of performing assays on whole cell systems, which can test the effect on cellular response (See col. 6, ln 1-19), as well as enzymatic assays, which test an enzyme's activity towards its substrate (See col. 6, ln 66- col. 7, ln 16) (Claim 32). Like most HTS systems, Parce et al's design is automated, making use of robotics and computers to quickly and efficiently perform the assays (Claim 34). The HTS assay system of Parce et al is ideal for screening compounds of such small quantities and particulate size, such as those produced in the method of Liversidge et al; therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a high throughput screening device designed specifically for microscale compounds, such as that by Parce et al. One would have been motivated to use the device of Parce et al because it is specifically designed for use with very small volumes, as are utilized in the current claimed invention. One would have expected success because Parce et al teach that their HTS system is capable of screening a wide variety of compounds, including pharmaceuticals, for activities such as solubility and bioavailability (See col. 4, ln 46-col. 5, ln 2).

With respect to the amount of time between steps (a)-(c) reducing the particle size of one or more candidate compounds in a small scale mill in the presence of attrition media (taught by Liversidge et al) and (d) screening the one or more nanoparticulate compounds in a conventional high throughput screening assay (taught by Parce et al), the amount of time would depend on how long the nanoparticles would remain stable at the reduced size without agglomerating. Liversidge et al use the various surface modifiers (surface stabilizers) to prevent agglomeration and aggregation, but they are silent on how long these modifiers are effective. Liversidge et al use the various surface modifiers (surface stabilizers) to prevent agglomeration and aggregation, but they

are silent on how long these modifiers are effective. However, it would have been obvious to one of ordinary skill in the art to use the reduced size drug substance (candidate compound) particles, produced by the method of Liversidge et al in the small scale mill of Reed et al, directly in a HTS assay, as described by Parce et al (Claim 33). One of ordinary skill in the art would have motivation to use the candidate compounds directly in a high throughput screening assay in order to expedite the screening process and more quickly find a lead candidate for further testing. One would have expected success because high throughput screening can be performed at any time, additionally, the claim does not require the candidate compound to be found effective, it only requires HTS assay to be performed, therefore the effect of the timing of the HTS assay on the candidate compound is not considered in the claimed method.

Alternatively, it would also have been obvious to one of ordinary skill in the art at the time the invention was made to first screen the raw candidate compounds in a HTS assay to determine if one or more candidate compounds exhibit a desired activity, such as described by Parce et al, and then perform the particle size reduction process of Liversidge et al, on the small scale mill of Reed et al, on only those candidate compounds which showed the desired activity (Claim 37). One would have been motivated to first perform the high throughput screening assay of Parce et al in order narrow the scope of candidate compounds to be milled, thus saving time and money, as high throughput screening is becoming increasingly facile and available. As stated above, the method of Parce et al is capable of performing automatic assays, enzymatic assays or whole cell assays, and assays on two or more compounds (See Parce et al col. 7, ln 23-55, col. 6, ln 1-19, and col. 6, ln 66- col. 7, ln 16) (Claims 38-40). One would expect success for the same reasons as stated above, Parce et al teach that their HTS system is capable of screening a wide variety of compounds, including pharmaceuticals, for activities such as solubility and bioavailability (See col. 4, ln 46-col. 5, ln 2), and screening prior to the particle size reduction of Liversidge et al, performed in the small scale mill of Reed et al with total dispersion volumes of

less than 15 mL, would have no effect on the method of Liversidge et al, it would only reduce the number of candidate compounds to be reduced in size.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 7-18, 20, 24, 27, 31-35 and 37-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-12, 17, 20-28, 85, 89, 92 and 94 of copending Application No. 10/177,163. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods claimed in the co-pending application fall into the scope of the methods claimed by the current application. Claims 1-28 of the copending application are directed to a method of milling small quantities of candidate compounds and then screening one or more of the reduced-size candidate compounds in a high-throughput screening assay. Though claims 1-28 of the copending application do not require the amount of candidate compound dispersion to be less than 15 mL, as required by the current application, it would have been obvious to one of ordinary skill in the art at the time the invention was made to manipulate the amount of candidate compound dispersion for optimization purposes based on the availability of the candidate compound and the size of the

milling apparatus being used. Additionally, though claims 1-28 of the copending application require the further step of screening the reduced-size candidate compounds in a HTS assay, which is not required by the present application, the additional step of HTS does not render the method of the copending application patentably distinct from the claimed method of the current application. The following list is provided for clarity:

Current claim 1 is unpatentable over claim 23 of co-pending application 10/177,163.

Current claim 7 is unpatentable over claim 2 of co-pending application 10/177,163.

Current claim 8 is unpatentable over claim 3 of co-pending application 10/177,163.

Current claim 9 is unpatentable over claim 24 of co-pending application 10/177,163.

Current claim 10 is unpatentable over claim 6 of co-pending application 10/177,163.

Current claim 11 is unpatentable over claim 23 of co-pending application 10/177,163.

Current claim 12 is unpatentable over claims 10 and 11 of co-pending application 10/177,163.

Current claim 13 is unpatentable over claim 12 of co-pending application 10/177,163.

Current claim 14 is unpatentable over claim 27 of co-pending application 10/177,163.

Current claim 15 is unpatentable over claim 28 of co-pending application 10/177,163.

Current claim 16 is unpatentable over claim 22 of co-pending application 10/177,163.

Current claim 17 is unpatentable over claim 20 of co-pending application 10/177,163.

Current claim 18 is unpatentable over claim 21 of co-pending application 10/177,163.

Current claim 20 is unpatentable over claim 17 of co-pending application 10/177,163.

Current claim 24 is unpatentable over claim 25 of co-pending application 10/177,163.

Current claim 27 is unpatentable over claim 26 of co-pending application 10/177,163.

Current claim 31 is unpatentable over claim 1 of co-pending application 10/177,163.

Current claim 32 is unpatentable over claim 4 of co-pending application 10/177,163.

Current claim 33 is unpatentable over claim 5 of co-pending application 10/177,163.

Current claim 34 is unpatentable over claim 7 of co-pending application 10/177,163.

Claims 85-113 of the copending application are directed to a method of screening candidate compounds in a high throughput screening assay for a desired activity, and then reducing the size of selected candidate compounds by milling small quantities of candidate compounds. Though claims 85-113 of the copending application do not require the amount of candidate compound dispersion to be less than 15 mL, as required by the current application, it would have been obvious to one of ordinary skill in the art at the time the invention was made to manipulate the amount of candidate compound dispersion for optimization purposes based on the availability of the candidate compound and the size of the milling apparatus being used. The following list is provided for clarity:

Current claim 37 is unpatentable over claim 85 of co-pending application 10/177,163.

Current claim 38 is unpatentable over claim 89 of co-pending application 10/177,163.

Current claim 39 is unpatentable over claim 92 of co-pending application 10/177,163.

Current claim 40 is unpatentable over claim 94 of co-pending application 10/177,163.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER